REMARKS

In response to the Office Action of March 17, 2008 requiring Restriction, Applicants **elect, with traverse, Group (I)** namely claims 22-34 and, specifically, as far as claim 30 is concerned, the Applicants **elect, with traverse, the subcutaneous implant containing the active ingredient only in the core.**

According to the Examiner, the invention *as listed in groups (I), (II) and (III) do not relate to a single general inventive concept under PCT rule 13.1 and 13.2 since, the common single inventive concept, according to the Examiner is:*

(1) a composition with a PLGA core containing a drug , coated with a PLGA coating ,

(2) is not new in view of Wang et al. (Pharmaceutical Research 1996 13(7):1059-1064) teaching an implant matrix composed of PLGA and the active 5-fluorouracil that is coated with the same PLGA polymer used to make the matrix see page 1059, column 2, paragraph 5, page 1060, column 1, paragraph 2.

1. Common single inventive concept

First of all, Applicants **respectfully traverse** that the common single inventive concept of the present invention is that reference at item (1) above, namely, a composition with :

- a PLGA core containing a drug ,

- coated with a PLGA containing coating.

The Examiner's characterization is not correct. Rather, the invention relates to **specific** compositions, namely, **subcutaneous implants** as claimed in claim 22, comprising:

- a core (i) **obtained by extrusion** comprising at least one active principle dispersed in a polymeric matrix essentially consisting of PLGA,

- a coating (ii) in **film form** comprising as the main component PLGA.

The subcutaneous implants differ, therefore, from the generic composition considered by the Examiner as the common single inventive concept, in the following respects:

(i) The core is obtained by extrusion,

(ii) The coating on the core is in film form.

The above differences are critical differences **as they result in specific final products with peculiar characteristics from a structural point of view.**

(i) The extrusion process involves heating the active ingredient and PLGA up to the melting of the polymer **followed by an instant solidification** as soon as the melt mixture issues from the extruder. It follows from the above that the core has a **continuous structure, similar therefore to that of "spaghetti".**

Therefore, having specified in claim 22 that the core is obtained by extrusion provides a clear indication that the core must have a continuous and homogeneous structure, **therefore excluding the possibility that the core is not continuous.**

(ii) Having specified in claim 22 that the coating is in film form it gives a clear indication that also the coating has a homogeneous structure.

It follows from the above that the common single inventive concept is therefore **more specific** than that considered by the Examiner.

2. Wang et al.

Wang et al. disclose implants for **the eyes** and **not** items to be subcutaneously implanted (see page 1060 right column: the paragraph (**"*in vivo* release study"),** whose core is prepared by a method encompassing the following steps :

- mixing either a 50/50 or 75/25 PLGA dichloromethane solution (0.5mg/ml) with 5FU powder, to produce a wet mass,
- drying in a vacuum oven at 50°C for 12 hrs,
- grinding the resulting dry solid, and,
- compressing the ground dry solid using flat punches (2.5mm) (see page 1060, left column, lines 1-7 and page 1059, right column, last two lines).

The core disclosed by Wang et al. is therefore **different and distinguishable and has no bearing at all** with respect to Applicants' extruded core contained in the presently claimed subcutaneous implants.

In fact , as pointed out above, the extrusion process involves heating the active ingredient and PLGA up **to the melting of the polymer,** followed by an instant solidification as soon as the melt mixture issues from the extruder, namely, operating conditions which bring about, as seen above, a core characterized by having a **continuous (spaghetti-like) structure.**

On the other hand, Wang discloses a core obtained by **mechanically aggregating** (by operating **a simple compression) a ground dry solid**. The core encompassed by Wang et al is therefore a mechanical aggregation of **discrete granules**, and therefore it does **not** have a continuous structure.

As confirmation of the differences in structure between a formulation obtained by extrusion and one obtained by compression of powders or granules, Applicants submit herewith page 1500 from *Remington's Pharmaceutical Sciences (18th Edition)* reporting the extrusion process and page 1644 and pages 1634-1635 relating to the compression of powders.

As further evidence of the difference in structure between the presently claimed subcutaneous implants and those disclosed by Wang et al, Applicants call the Examiner's attention to the uncoated matrix disclosed in Wang et al., namely, MT, which completely

releases the drug, namely fluororacyl, **within 5 hours** (see figure 2 of Wang et al.), whereas the uncoated matrix containing the active ingredient obtained by extrusion in the subcutaneous implants of the instant invention releases the active ingredient over periods of time on the order of **months,** and respectively:

- within 150 days **(about 5 months)** (Figure 1 B relating to example 1 of the specification, wherein the drug is avoreline);
- 28 days **(about 1 month)** (Figure 2B relating to the example 2 of the specification, wherein the drug is sodium ethidronate); and,
- within 100 days **(more than 3 months)** (Figure 3 B relating to example 3 of the specification, wherein the drug is again avoreline).

It follows, therefore, that the coated implants disclosed in Wang et al. **in no way** detract or take away from the novelty of the instant subcutaneous implants.

Finally, Applicants respectfully conclude that the subcutaneous implants as claimed in claim 1 besides being novel are also **unobvious.**

The target of the present invention resides in Applicants having found subcutaneous implants which possess:

- a **reduced** "burst" release of the active ingredient in **the first days** after the subcutaneous implant are introduced into the human body, and
- **a reduced second burst** caused by the disintegration of the core (see page 4, line 9, and page 5, line 1 of the specification).

As can be seen above, Wang et al. deal with a different implant, destined for a different type of administration, and, moreover, having a core which is obtained by the compression of granules of PLGA and active ingredient. The core of Wang et al. is coated with PLGA with the purpose of slowing the release of fluorouracil for a period of **up to 25 hours** (see figure 2).

In addition, noting the results from figure 1, the implants disclosed in Wang et al. are **not completely coated** (see CM1 wherein the coated matrix contains a hole drilled through the implant and CM2 contains a hole drilled through the coating on one side.)

It follows from the foregoing that one of ordinary skill in the art would not have been motivated to believe ***in any way*** that it was possible to reduce the aforementioned burst release specifically connected to the subcutaneous implants obtained by extrusion by coating the same with a film containing PLGA as taught by Wang et al. which moreover teaches to **partially** coat with PLGA a PLGA core obtained **via a completely different technique** resulting in a completely different **release profile of the active ingredient** from that contemplated by the instantly claimed invention.

Withdrawal of the Restriction Requirement is earnestly solicited.

Also, in view of the foregoing, Applicants deem that the claimed invention is novel and unobvious and the issuance of a Notice of Allowance is respectfully requested.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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Remington's Pharmaceutical Sciences . . . *a treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also a guide to the professional responsibilities of the pharmacist as the drug-information specialist of the health team . . . . A textbook and reference work for pharmacists, physicians and other practitioners of the pharmaceutical and medical sciences.*

Eighteenth Edition—1990

Published in the 170th year of the
PHILADELPHIA COLLEGE OF PHARMACY AND SCIENCE

Antioxidants are a special type of stabilizer used primarily to assist in retarding oxidation. Under certain environmental conditions, these materials, too, can migrate to the surface of the polymer. Also, combinations of antioxidants with other additives may result in undesirable chemical reactions.

Antistatic agents are used to prevent the buildup of static charges on the plastic surface.

Slip agents are added primarily to polyolefins (polyethylene and polypropylene) in order to reduce the coefficient of friction of the material. These particular chemicals result in antitack and antiblock characteristics in the end product.

Dyes and pigments are added to impart color. As with many other additives, both dyes and pigments may be leached or solubilized into the product.

Thus, there are a number of additives used in the preparation of plastic packaging materials, and it is quite possible and probable that an additive could be extracted during use. Therefore, it is essential that the final product/package be evaluated for safety and stability. Evaluations should be conducted with the product under various time and storage conditions. Wherever possible, conditions simulating those to which the product is expected to be subjected should be evaluated. Evaluations under varying storage conditions should not only take into consideration the chemical compatibility of the product with the package but also include an investigation of the compatibility of the primary plastic container with its secondary packaging (since it is possible that, although the product could be compatible with its immediate container, incompatibilities could exist between the primary and secondary packaging, thereby resulting in an incompatible substance in the final product). Crazing and stress-cracking of plastic packaging, which could arise due to product and/or environmental attack, also should be considered. Prolonged exposure to ultraviolet light has been shown to enhance the migration of certain additives which, in turn, can accelerate the aging characteristics of the plastic and decrease the shelf life of the product. In some instances, incompatibilities that might occur readily can be detected visually; in others, sophisticated extraction techniques must be followed in order to ascertain the effects storage conditions may have had. For this reason, well-planned stability studies (ie, time and temperature of storage) need to be established.

Processing

As already stated, additives are used to modify the properties of a plastic. In addition, the manner in which a plastic is formed into the desired configuration can affect the end properties. It is important that process parameters, such as temperature, pressure and time, be controlled rigidly to insure batch-to-batch uniformity for plastic objects. If process parameters are not controlled adequately, such deleterious effects on plastic properties as thermal degradation, piece-part stresses and incorrect physical dimensions may result. Process thermal degradation of a plastic (or additive modified plastic formulation) can affect the leaching characteristics of the plastic object, its permeation characteristics and its long-term stability during the shelf life of the pharmaceutical product. Piece-part stresses may be relieved when the pharmaceutical package is subjected to certain environmental conditions resulting in package failure during the shelf life of the product.

The more common plastic processing methods employed for pharmaceutical packaging components follow.

Injection Molding

Injection molding is an intermittent process, the plastic being heated to a melted or viscous state and then forced into a cavity (mold) at high pressure. The melted material cools in the cavity and solidifies. The mold is then opened and the part removed. A wide range of thermoplastic a several thermosetting materials can be injection-mold Very intricate configurations can be obtained by injecti molding of plastics.

Extrusion

Extrusion is a continuous process, the plastic being heat to a melted or viscous state and forced under pressu through a die, resulting in a configuration of desired shar The extruded profile is cooled to a solid state, generally spraying with water, by immersion in water or by usi chilled rolls for film material. A wide range of thermopla tic materials can be extruded. Typical extruded profil used by the pharmaceutical industry are packaging film and medical tubing. Plastic packaging film also is forme by blow extrusion, an extruded tube being blown into a larg cylinder and then slit after cooling.

Blow Molding

The plastic is heated to a melted or viscous state an formed into a hollow cylinder (parison). The parison gener ally is extruded, but may be injection-molded. If extruded the parison is cut to the required length and transferred t the blowing cavity (mold). The bottom of the parison i pinched off by the mold and air is blown into the parison expanding the viscous plastic to the walls of the cavity, thu forming the desired shape of the container. The melted material cools in the cavity and solidifies. The mold i opened and the container removed. Pharmaceutical bottles are blow-molded from a wide range of thermoplastic materials, of which polyethylene and polypropylene are used predominantly.

Compression Molding

Compression molding is used for thermosetting materials and is an intermittent process. The thermosetting material (powder or a tablet preform) is placed into a heated cavity (mold). The material melts and flows to fill the cavity. The mold is held under pressure until the thermosetting material cures, after which the mold is opened and the part removed. As with injection molding, very intricate configurations can be obtained by compression-molding of thermosetting materials.

Types and Uses

The following types of plastics are used commonly in health-care practice; several of their properties and end uses are indicated.

Thermoplastics

The following are used commonly in injection molding, blow molding, extrusion and fabricated sheeting.

Acrylics—This class includes the polymethacrylates, polyacrylates and copolymers of acrylonitrile. There are many variations in this class, mainly concerned with the combinations of methacrylate and acrylate esters, as well as acrylonitrile. These plastics are characterized by clarity and unusual optical properties, low water absorption, good electrical resistivity, excellent weatherability and fair tensile strength. Their heat resistance is low and care should be taken to keep them below temperatures of 200°F, at which they tend to soften. Acrylics find considerable use in a multiplicity of devices employed in today's hospitals and clinics. A specific application is in the adapters used in solution-administration sets and blood-collection sets.

Cellulosics—The members of this class are available in a

Sugar-Coated Tablets (SCT)—These are compressed tablets containing a sugar coating. Such coatings may be colored and are beneficial in covering up drug substances possessing objectionable tastes or odors, and in protecting materials sensitive to oxidation.

Film-Coated Tablets (FCT)—These are compressed tablets which are covered with a thin layer or film of a water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating with the added advantage of a greatly reduced time period required for the coating operation.

Enteric-Coated Tablets (ECT)—These are compressed tablets coated with substances that resist solution in gastric fluid but disintegrate in the intestine. Enteric coatings can be used for tablets containing drug substances which are inactivated or destroyed in the stomach, for those which irritate the mucosa or as a means of delayed release of the medication.

Multiple Compressed Tablets (MCT)—These are compressed tablets made by more than one compression cycle.

Layered Tablets—Such tablets are prepared by compressing additional tablet granulation on a previously compressed granulation. The operation may be repeated to produce multilayered tablets of two or three layers. Special tablet presses are required to make layered tablets such as the Versa press (*Stokes/Pennwalt*).

Press-Coated Tablets—Such tablets, also referred to as dry-coated, are prepared by feeding previously compressed tablets into a special tableting machine and compressing another granulation layer around the preformed tablets. They have all the advantages of compressed tablets, ie, slotting, monogramming, speed of disintegration, etc, while retaining the attributes of sugar-coated tablets in masking the taste of the drug substance in the core tablets. An example of a press-coated tablet press is the *Manesty* Drycota. Press-coated tablets also can be used to separate incompatible drug substances; in addition, they can provide a means to give an enteric coating to the core tablets. Both types of multiple-compressed tablets have been used widely in the design of prolonged-action dosage forms.

Controlled-Release Tablets—Compressed tablets can be formulated to release the drug slowly over a prolonged period of time. Hence, these dosage forms have been referred to as "Prolonged-Release" or "Sustained-Release" dosage forms as well. These tablets (as well as capsule versions) can be categorized into three types: (1) those which respond to some physiological condition to release the drug, such as enteric coatings; (2) those that release the drug in a relatively steady, controlled manner and (3) those that combine combinations of mechanisms to release "pulses" of drug, such as repeat-action tablets. The performance of these systems are described in more detail in Chapter 91.

Tablets for Solution—Compressed tablets to be used for preparing solutions or imparting given characteristics to solutions must be labeled to indicate that they are not to be swallowed. Examples of these tablets are Halazone Tablets for Solution and Potassium Permanganate Tabl for Solution.

Effervescent Tablets—In addition to the drug substance, these co tain sodium bicarbonate and an organic acid such as tartaric or citric. the presence of water, these additives react liberating carbon dioxi which acts as a distintegrator and produces effervescence. Except f small quantities of lubricants present, effervescent tablets are soluble.

Compressed Suppositories or Inserts—Occasionally, vaginal su positories, such as Metronidazole Tablets, are prepared by compressio Tablets for this use usually contain lactose as the diluent. In this cas as well as for any tablet intended for administration other than b swallowing, the label must indicate the manner in which it is to be used

Buccal and Sublingual Tablets—These are small, flat, oval tablets Tablets intended for buccal administration by inserting into the bucca pouch may dissolve or erode slowly; therefore, they are formulated anc compressed with sufficient pressure to give a hard tablet. Progesterone Tablets may be administered in this way.

Some newer approaches use tablets that melt at body temperatures. The matrix of the tablet is solidified while the drug is in solution. After melting, the drug is automatically in solution and available for absorption, thus eliminating dissolution as a rate-limiting step in the absorption of poorly soluble compounds. Sublingual tablets, such as those containing nitroglycerin, isoproterenol hydrochloride or erythrityl tetranitrate, are placed under the tongue. Sublingual tablets dissolve rapidly and the drug substances are absorbed readily by this form of administration.

Molded Tablets or Tablet Triturates (TT)

Tablet triturates usually are made from moist material using a trit- urate mold which gives them the shape of cut sections of a cylinder. Such tablets must be completely and rapidly soluble. The problem arising from compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing Tablets (DT)—These tablets provide a convenient quantity of potent drug that can be incorporated readily into powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic Tablets (HT)—Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now available for most drug substances, there is no justification for the use of hypodermic tablets for injection. Their use in this manner should be discouraged since the resulting solutions are not sterile. Large quantities of these tablets continue to be made but for oral administration. No hypodermic tablets have ever been recognized by the official compendia.

Compressed Tablets (CT)

In order for medicinal substances, with or without diluents, to be made into solid dosage forms with pressure, using available equipment, it is necessary that the material, either in crystalline or powdered form, possess a number of physical characteristics. These characteristics include the ability to flow freely, cohesiveness and lubrication. Other ingredients such as disintegrants designed to break the tablet up in gastrointestinal fluids, and controlled-release polymers designed to slow down drug release, ideally should possess these characteristics, or not interfere with the desirable performance traits of the other excipients. Since most materials have none or only some of these properties, methods of tablet formulation and preparation have been developed to impart these desirable characteristics to the material which is to be compressed into tablets.

The basic mechanical unit in all tablet-compression equipment includes a lower punch which fits into a die from the bottom and an upper punch, having a head of the same shape and dimensions, which enters the die cavity from the top after the tableting material fills the die cavity. See Fig 89-2. The tablet is formed by pressure applied on the punches and subsequently is ejected from the die. The weight of the tablet is determined by the volume of the material which fills the die cavity. Therefore, the ability of the granulation to flow freely into the die is important in insuring a uniform fill, as well as the continuous movement of the granulation from the source of supply or feed hopper.

If the tablet granulation does not possess cohesive properties, the tablet after compression will crumble and fall apart on handling. As the punches must move freely within the die and the tablet must be ejected readily from the punch faces, the material must have a degree of lubrication to minimize friction and allow for the removal of the compressed tablets.

There are three general methods of tablet preparation: the wet-granulation method, the dry-granulation method and direct compression. The method of preparation and

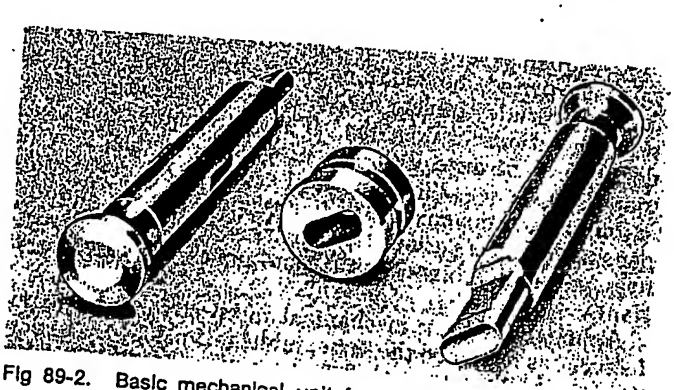

Fig 89-2. Basic mechanical unit for tablet compression: lower punch, die and upper punch (courtesy, Vector/Colton).

the added ingredients are selected in order to give the tablet formulation the desirable physical characteristics allowing the rapid compression of tablets. After compression the tablets must have a number of additional attributes such as appearance, hardness, disintegration ability, appropriate dissolution characteristics and uniformity which also are influenced both by the method of preparation and by the added materials present in the formulation. In the preparation of compressed tablets the formulator also must be cognizant of the effect which the ingredients and methods of preparation may have on the availability of the active ingredients and hence the therapeutic efficacy of the dosage form. In response to a request by physicians to change a dicumarol tablet in order that it might be broken more easily, a Canadian company reformulated to make a large tablet with a score. Subsequent use of the tablet containing the same amount of drug substance as the previous tablet, resulted in complaints that larger-than-usual doses were needed to produce the same therapeutic response. On the other hand, literature reports indicate that the reformulation of a commercial digoxin tablet resulted in a tablet, although containing the same quantity of drug substance, that gave the desired clinical response at half its original dose. Methods and principles that can be used to assess the effects of excipients and additives on drug absorption have been reviewed.[2,14,15] See Chapters 36, 75 and 76.

Tablet Ingredients

In addition to the active or therapeutic ingredient, tablets contain a number of inert materials. The latter are known as additives or *excipients*. They may be classified according to the part they play in the finished tablet. The first group contains those which help to impart satisfactory processing and compression characteristics to the formulation. These include diluents, binders and glidants and lubricants. The second group of added substances helps to give additional desirable physical characteristics to the finished tablet. Included in this group are disintegrants, colors, and in the case of chewable tablets, flavors and sweetening agents, and in the case of controlled-release tablets, polymers or waxes or other solubility-retarding materials.

Although the term *inert* has been applied to these added materials, it is becoming increasingly apparent that there is an important relationship between the properties of the excipients and the dosage forms containing them. Preformulation studies demonstrate their influence on stability, bioavailability and the processes by which the dosage forms are prepared. The need for acquiring more information and use standards for excipients has been recognized in a joint venture of the Academy of Pharmaceutical Sciences and the Council of the Pharmaceutical Society of Great Britain. The result is called the *Handbook of Pharmaceutical Excipients*. This reference is now distributed widely throughout the world.[16]

Diluents

Frequently the single dose of the active ingredient is small and an inert substance is added to increase the bulk in order to make the tablet a practical size for compression. Compressed tablets of dexamethasone contain 0.75 mg steroid per tablet; hence, it is obvious that another material must be added to make tableting possible. Diluents used for this purpose include dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, mannitol, sodium chloride, dry starch and powdered sugar. Certain diluents, such as mannitol, lactose, sorbitol, sucrose and inositol, when present in sufficient quantity, can impart properties to some compressed tablets that permit disintegration in the mouth by chewing. Such tablets commonly are called *chewable tablets*. Upon chewing, properly prepared tablets will disintegrate smoothly at a satisfactory rate, have a pleasant taste and feel and leave no unpleasant aftertaste in the mouth. Diluents used as excipients for direct compression formulas have been subjected to prior processing to give them flowability and compressibility. These are discussed under *Direct Compression*, page 1645.

Most formulators of immediate-release tablets tend to use consistently only one or two diluents selected from the above group in their tablet formulations. Usually, these have been selected on the basis of experience and cost factors. However, in the formulation of new therapeutic agents the compatibility of the diluent with the drug must be considered. For example, calcium salts used as diluents for the broad-spectrum antibiotic tetracycline have been shown to interfere with the drug's absorption from the gastrointestinal tract. When drug substances have low water solubility, it is recommended that water-soluble diluents be used to avoid possible bioavailability problems. Highly adsorbent substances, eg, bentonite and kaolin, are to be avoided in making tablets of drugs used clinically in small dosage, such as the cardiac glycosides, alkaloids and the synthetic estrogens. These drug substances may be adsorbed to the point where they are not completely available after administration. The combination of amine bases with lactose, or amine salts with lactose in the presence of an alkaline lubricant, results in tablets which discolor on aging.

Microcrystalline cellulose (Avicel) usually is used as an excipient in direct compression formulas. However, its presence in 5 to 15% concentrations in wet granulations has been shown to be beneficial in the granulation and drying processes in minimizing case-hardening of the tablets and in reducing tablet mottling.

Many ingredients are used for several different purposes, even within the same formulation. For example, corn starch can be used in paste form as a binder. When added in drug or suspension form, it is a good disintegrant. Even though these two uses are to achieve opposite goals, some tablet formulas use corn starch in both ways. In some controlled-release formulas, the polymer hydroxypropylmethylcellulose (HPMC) is used both as an aid to prolong the release from the tablet, as well as a film-former in the tablet coating. Therefore, most excipients used in formulating tablets and capsules have many uses, and a thorough understanding of their properties and limitations is necessary in order to use them rationally.

Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. They impart a cohesiveness to the tablet formulation which insures the tablet remaining intact after compression, as well as improving the free-flowing qualities by the formulation of granules of desired hardness and size. Materials commonly used as binders include starch, gelatin and sugars as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums which have been used include acacia, sodium alginate, extract of Irish moss, panwar gum, ghatti gum, mucilage of isapol husks, carboxymethylcellulose, methylcellulose, polyvinylpyrrolidone, Veegum and larch arabogalactan. Other agents which may be considered binders under certain circumstances are polyethylene glycol, ethylcellulose, waxes, water and alcohol.

The quantity of binder used has considerable influence on the characteristics of the compressed tablets. The use of too much binder or too strong a binder will make a hard tablet which will not disintegrate easily and which will cause excessive wear of punches and dies. Differences in binders used

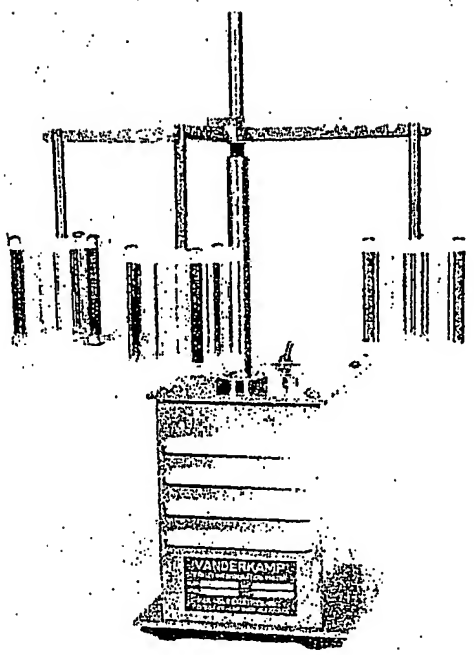

Fig 89-5. Vanderkamp Tablet Disintegration Tester (courtesy, Van-Kel).

test is indicated when any residue remaining is a soft mass having no palpably soft core. The plastic discs help to force any soft mass which forms through the screen.

For compressed uncoated tablets the testing fluid is usually water at 37°, but in some cases the monographs direct that Simulated Gastric Fluid TS be used. If one or two tablets fail to disintegrate, the test is to be repeated using 12 tablets. Of the 18 tablets then tested, 16 must have disintegrated within the given period of time. The conditions of the test are varied somewhat for coated tablets, buccal tablets and sublingual tablets. Disintegration times are included in the individual tablet monograph. For most uncoated tablets the period is 30 min although the time for some uncoated tablets varies greatly from this. For coated tablets up to 2 hr may be required, while for sublingual tablets, such as CT Isoproterenol Hydrochloride, the disintegration time is 3 min. For the exact conditions of the test, consult the USP.

Dissolution Test

For certain tablets the monographs direct compliance with limits on dissolution rather than disintegration. Since drug absorption and physiological availability depend on having the drug substance in the dissolved state, suitable dissolution characteristics are an important property of a satisfactory tablet. Like the disintegration test, the dissolution test for measuring the amount of time required for a given percentage of the drug substance in a tablet to go into solution under a specified set of conditions is an *in vitro* test. It is intended to provide a step towards the evaluation of the physiological availability of the drug substance, but as described currently, it is not designed to measure the safety or efficacy of the tablet being tested. Both the safety and effectiveness of a specific dosage form must be demonstrated initially by means of appropriate *in vivo* studies and clinical evaluation. Like the disintegration test, the dissolution test does provide a means of control in assuring that a given tablet formulation is the same as regards dissolution as the batch of tablets shown initially to be clinically effective. It also provides an *in vitro* control procedure to eliminate variations among production batches. Refer to Chapter 31 for a complete discussion of dissolution testing.

Validation

In this era of increasing regulatory control of the pharmaceutical industry, manufacturing procedures cannot be discussed without the mention of some process validation activity. By way of documentation, product testing and, perhaps, in-process testing as well, the manufacturer can demonstrate that his formula and process perform in the manner expected and that it does so reproducibly.

Although the justification for requiring validation is found in the regulations relating to "Current Good Manufacturing Practices for Finished Pharmaceuticals" as well as other sources, there is still much room for interpretation and the process varies from one company to another. General areas of agreement appear to be that

The validation activity must begin in R&D and continue through product introduction.
Documentation is the key.
In general, three batches represent an adequate sample for validation.

Increasingly, the FDA is rejecting historical data or "retrospective validation and is requiring that new products be validated from beginning to end, a process called "prospective validation."

Methods of Preparation

Wet-Granulation Method

The most widely used and most general method of tablet preparation is the wet-granulation method. Its popularity is due to the greater probability that the granulation will meet all the physical requirements for the compression of good tablets. Its chief disadvantages are the number of separate steps involved, as well as the time and labor necessary to carry out the procedure, especially on the large scale. The steps in the wet method are weighing, mixing, granulation, screening the damp mass, drying, dry screening, lubrication and compression. The equipment involved depends on the quantity or size of the batch. The active ingredient, diluent and disintegrant are mixed or blended well. For small batches the ingredients may be mixed in stainless steel bowls or mortars. Small-scale blending also can be carried out on a large piece of paper by holding opposite edges and tumbling the material back and forth. The powder blend may be sifted through a screen of suitable fineness to remove or break up lumps. This screening also affords additional mixing. The screen selected always should be of the same type of wire or cloth that will not affect the potency of the ingredients through interaction. For example, the stability of ascorbic acid is affected deleteriously by even small amounts of copper, thus care must be taken to avoid contact with copper or copper-containing alloys.

For larger quantities of powder the Patterson-Kelley twin-shell blender and the double-cone blender offer means of precision blending and mixing in short periods of time (Fig 89-6). Twin-shell blenders are available in many sizes from laboratory models to large production models. Planetary mixers, eg, the Glen mixer and the Hobart mixer, have served this function in the pharmaceutical industry for many years (Fig 89-7). On a large scale, ribbon blenders also are employed frequently and may be adapted for continuous production procedures. Mass mixers of the sigma-blade type have been used widely in the pharmaceutical industry.

Rapidly increasing in popularity are the high-speed, high-shear mixers such as the Lodige/Littleford, the Diosna, the Fielder and the Baker-Perkins. For these mixers a full range of sizes are available. The processing of granulations in these machines is generally faster than in conventional granulators. However, control over the process is critical, and scale-up issues may become extremely important.[25]

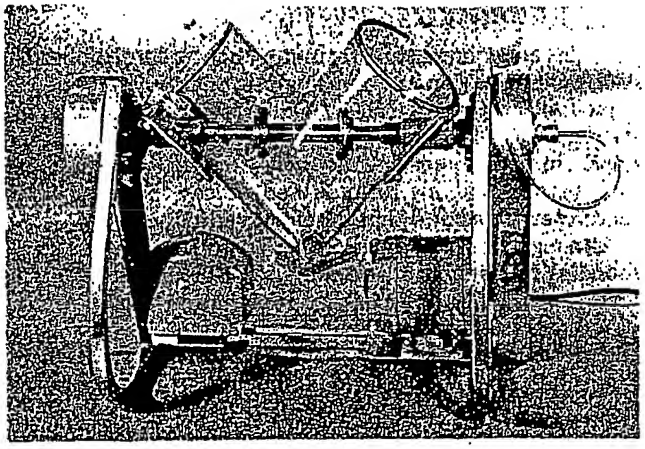

Fig 89-6. Twin-shell blender for solids or liquid–solids blending (courtesy, Patterson-Kelley).

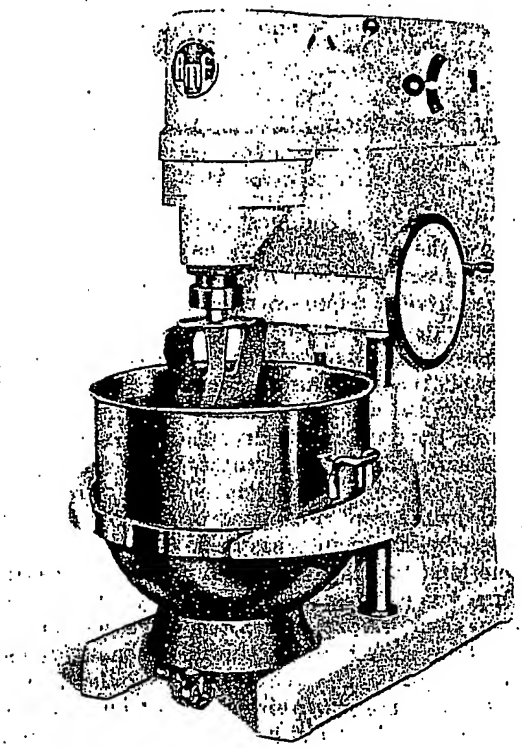

Fig 89-7. The Glen powder mixer (courtesy, Am Machine).

Fluid-bed granulation (discussed below) also is gaining wide acceptance in the industry. For both of these types of processing, slight modifications to the following procedures are required.

Solutions of the binding agent are added to the mixed powders with stirring. The powder mass is wetted with the binding solution until the mass has the consistency of damp snow or brown sugar. If the granulation is overwetted, the granules will be hard, requiring considerable pressure to form the tablets, and the resultant tablets may have a mottled appearance. If the powder mixture is not wetted sufficiently, the resulting granules will be too soft, breaking down during lubrication and causing difficulty during compression.

The wet granulation is forced through a 6- or 8-mesh screen. Small batches can be forced through by hand using a manual screen. For larger quantities one of several comminuting mills suitable for wet screening can be used. These include the Stokes oscillator, the Colton rotary granulator, the Fitzpatrick comminuting mill or the Stokes oscillator mill. See Fig 89-8. In comminuting mills the granulation is forced through the sieving device by rotating hammers, knives or oscillating bars. Most high-speed mixers are equipped with a chopper blade which operates independently of the main mixing blades and can replace the wet milling step, ie, can obviate the need for a separate operation.

For tablet formulations where continuous production is justified, extruders such as the Reitz extructor have been adapted for the wet-granulation process. The extruder consists of a screw mixer with a chamber where the powder is mixed with the binding agent and the wet mass gradually is forced through a perforated screen forming threads of the wet granulation. The granulation then is dried by conventional methods. A semiautomatic continuous process using the Reitz extructor has been described for the preparation of the antacid tablet Gelusil (*Warner-Lambert*).

Moist material from the wet milling step is placed on large sheets of paper on shallow wire trays and placed in drying cabinets with a circulating air current and thermostatic heat control. See Fig 89-9. While tray drying was the most widely used method of drying tablet granulations until recently, fluid-bed drying is now equally popular. Notable among the newer methods being introduced are the fluid-

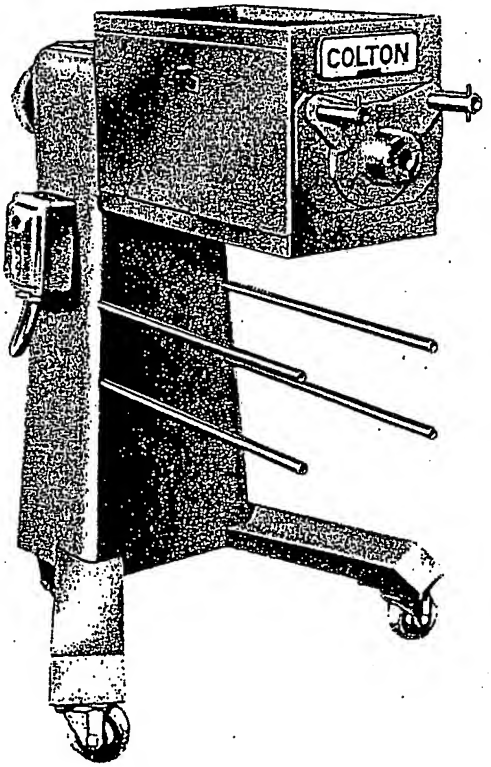

Fig 89-8. Rotary granulator and sifter (courtesy, Vector/Colton).

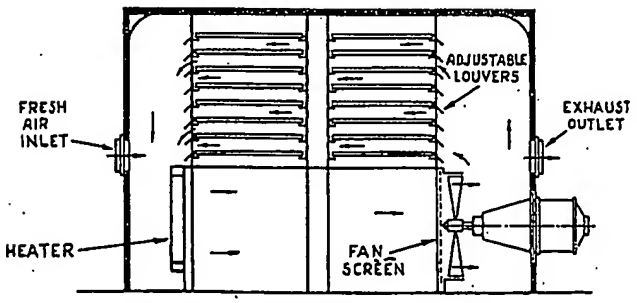

Fig 89-9. Cross section of tray dryer.